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Associations of transthoracic echocardiographic features with cardioembolic stroke among patients without atrial fibrillation

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OBJECTIVES/SPECIFIC AIMS: To identify cardiac structural and function parameters, obtained on usual stroke-care TTE evaluation, associated with cardioembolic stroke (CE) in patients without AF. Hypothesis—left atrial (LA) size and valve dysfunction will be strongly associated with incident CE. **METHODS/STUDY POPULATION:** Inclusion criteria: July 1, 2013 to July 1, 2015 admission with imaging-confirmed ischemic stroke, no AF, TTE within 1st 7 days. TTE structure/function parameters were recorded. Stroke subtype (CE vs. other) defined using TOAST criteria, blinded to TTE. New AF definition: AF on ECG, telemetry or event monitor. CE/New AF outcome of interest in separate multivariable logistic regression models testing associations with TTE parameters (adjusting for demographics/vascular risk factors). **RESULTS/ANTICIPATED RESULTS:** Participants ($n = 332$) were ~60 years hypertensive black males with moderate NIHSS and normal ejection fraction. In adjusted models, odds of CE increased with increasing LA systolic diameter (per 0.1 cm), mitral E point velocity (cm/s), mitral valve dysfunction, wall motion abnormality. New AF also associated with increasing LA systolic diameter. **DISCUSSION/SIGNIFICANCE OF IMPACT:** These findings may suggest cardiac structural changes independent of AF that are on the CE causal pathway. Understanding the relationship between such TTE parameters and stroke subtype would impact clinical practice, as such TTE data is underutilized when considering stroke mechanism and management.

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Augmenting perception through direct electrical stimulation of adult somatosensory cortex

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OBJECTIVES/SPECIFIC AIMS: Our main objectives are to study sensory encoding in the adult cortex and quantify rodents' ability to use intracortical microstimulation to guide behavior. **METHODS/STUDY POPULATION:** Three rats were implanted with unilateral bipolar stimulating electrodes. The electrodes were connected to a wireless neural stimulator housed in the rat's backpack. The rat's swim path was tracked by a video camera above the circular pool, and stimulation parameters were updated in real-time based on distance from the platform. Stimulation was delivered as the distance from the platform increased. Stimulation amplitude was determined through behavioral threshold testing, and parameters ranged from 15–75 μ A with 100-Hz pulse trains and 0.2-ms pulses. Rats were first challenged with the 4-platform task in which the submerged platform was randomized across 4 possible locations. This dissociated visual cues from the platform location, as rats had knowledge of the 4 possible locations, but had to use stimulation to guide them efficiently. Next, rats were tasked with the more challenging random-platform task. Visual cues were completely dissociated from the platform location by randomizing the platform location across the entire pool. Performance using the neuroprosthetic device was assessed by comparing trials when the device was on (stimulation trial) Versus off (no-stim trial) for the 2 tasks. **RESULTS/ANTICIPATED RESULTS:** *4-platform task:* Rats visited less potential platform locations when the neuroprosthetic was on Versus off. Rats were also more likely to visit the correct platform location on their first swim trajectory when brain stimulation was delivered. When artificial cues were not available, rats had a greater chance of visiting the platform location from the previous trial. This indicated that rats relied on visuospatial memory without the neuroprosthetic. *Random platform task:* Performance was measured by taking the ratio of the rat's actual path length to the optimal path length. When the neuroprosthetic was on, rats demonstrated superior performance through a smaller path to length ratio compared with when the device was off. The platform locations of catch trials were matched to a random subset of stimulation trials, permitting a paired sample *t*-test. Both rats had significantly shorter path lengths when the device was on. **DISCUSSION/SIGNIFICANCE OF IMPACT:** Rodents have excellent navigation skills that have been well studied. They have been shown to rely on multimodal sensory information from visual, olfactory, auditory, and idiothetic cues to navigate through their environment. The importance of these cues depends on both their environmental presence and task relevance. In the original Morris water maze experiment, rats use vision to form a visuospatial map of the platform location for allocentric navigation. Here, we have shown that sensory augmented rats can pick up on novel sensory information delivered through ICMS to efficiently find a hidden platform when visual cues are made

irrelevant. Our results have implications for the design of the bi-directional sensorimotor neuroprosthetic. We have demonstrated that mammals can interpret artificial sensory information to guide behavior. Future directions include investigating sensory encoding in other primary sensory areas and downstream targets along the somatosensory neuraxis.

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Authors' perceptions of the interdisciplinarity of their research

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OBJECTIVES/SPECIFIC AIMS: The objectives of this study were to compare different methods for determining the disciplines involved in a research article. We sought to address the following questions: To what extent does the number of disciplines reported by an article's corresponding author agree with their description of the article as unidisciplinary or interdisciplinary? (Q1) and To what extent does the corresponding author's description of the research as unidisciplinary or interdisciplinary agree with its classification as unidisciplinary or interdisciplinary based on the affiliation of its co-authors? (Q2). **METHODS/STUDY POPULATION:** Using Scopus, we randomly selected 100 articles from 2010 and 2015 from science teams that had at least 1 author affiliated with Johns Hopkins. Author affiliations were grouped into common academic disciplines: Basic Science, Medicine (and all clinical specialties), Public Health, Engineering, Social Science, Computer Science, Pharmacy, Nursing, and Other. Articles with more than 1 discipline were considered, interdisciplinary. We then sent an online Qualtrics survey to the corresponding author of each article and asked them to indicate (1) all of the disciplines that contributed to the research article at hand, and (2) to indicate whether they considered the research to be "unidisciplinary" or "interdisciplinary" based on definitions that we provided. **RESULTS/ANTICIPATED RESULTS:** For Q1, we asked corresponding authors to indicate the number of disciplines involved in their research and then to choose the definition that best described their research. Among 76 respondents, 42 indicated that their research consisted of 1 discipline, and 34 indicated that their research consisted of more than 1 discipline. Of the 42 respondents who indicated that their research consisted of one discipline, 21 (50%) respondents described their research as "unidisciplinary" and 21 (50%) described their research as "interdisciplinary." However, of the 34 respondents who indicated that their research consisted of more than 1 discipline, all but 1 (97%) described their research as "interdisciplinary." For Q2, we assigned a discipline to each co-author based on his/her affiliation and counted the number of disciplines involved. Among 76 respondents, of the 22 who described their research as "unidisciplinary," 16 (73%) were categorized as "unidisciplinary" and 6 (27%) were categorized as "interdisciplinary," using this method. Of the 54 respondents who described their research as "interdisciplinary," 30 (56%) were categorized as "interdisciplinary" and 24 (44%) as "unidisciplinary." **DISCUSSION/SIGNIFICANCE OF IMPACT:** Our results highlight that different methods for determining whether a given research article is interdisciplinary are likely to yield different results. Even when researchers indicate that their research is based within one major discipline, they may still consider it interdisciplinary. Likewise, classifying an article as either unidisciplinary or interdisciplinary based on the affiliations of its co-authors, may not be consistent with the way it is viewed by its authors. It is important to acknowledge that assessing the interdisciplinarity of research is complex and that objective and subjective views may differ.

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Beyond diagnosis: Using ultrasound to affect tumor vasculature for hepatocellular carcinoma (HCC) therapy

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OBJECTIVES/SPECIFIC AIMS: Preliminary animal studies showed that low-intensity ultrasound (US) coincident with intravascularly administered microbubbles locally disrupts tumor vasculature. This study translates the novel therapy of antivasculature ultrasound (AVUS) into an autochthonous model of hepatocellular carcinoma (HCC). The differential effects produced by AVUS at low and high doses are evaluated. **METHODS/STUDY POPULATION:** HCC was induced in 12 Wistar rats by ingestion of 0.01% diethylnitrosamine in drinking water for 12 weeks. Rats received AVUS treatment at low and high doses. Low dose group ($n = 6$) received 1 W/cm² US for 1 minute with 0.2 mL microbubbles injected IV.

High dose group ($n=6$) received $2W/cm^2$ for 2 minute with 0.7 mL microbubbles IV. Perfusion was measured before and after AVUS with contrast-enhanced ultrasound (CE-US) and power Doppler (PD-US). Peak enhancement (PE) and perfusion index (PI) were measured from each US mode. Histology after sacrifice or natural death was compared to pre/post US. Analysis of H&E and trichrome sections was evaluated for percent area of hemorrhage and findings of tissue injury and repair including inflammation, necrosis, and fibrosis. RESULTS/ANTICIPATED RESULTS: After high dose AVUS, PE, and PI of CE-US decreased from baseline by an average of 33.3% and 29.7%, respectively. Histology showed extensive tissue injury (hemorrhage, necrosis, fibrosis) in 58% of tumor cross-sectional area. Conversely, low dose AVUS increased PE and PI of CE-US by an average of 39.3% and 67.8%, respectively. Histology showed smaller areas of microhemorrhage versus large pools of hemorrhage (only 17% area). PD-US changes were similar to CE-US. DISCUSSION/SIGNIFICANCE OF IMPACT: In summary, the opposing effects of AVUS observed at 2 doses allows for multiple roles in tumor therapy. Enhanced perfusion at a low dose may improve drug delivery or radiation therapy. Whereas, vascular disruption at high doses of AVUS may allow noninvasive ischemic therapy. Furthermore, AVUS is ripe for translation given the use its component parts clinically: low-intensity long-tone burst for physiotherapy and microbubbles as an US contrast agent. Thus, AVUS should be evaluated for translation of its differential effects into noninvasive therapies for HCC and other tumors.

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Cardiac injury due to *Streptococcus pneumoniae* invasion during severe pneumococcal pneumonia in a novel nonhuman primate model

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OBJECTIVES/SPECIFIC AIMS: The aims of this study are (1) to develop and characterize a novel nonhuman primate model of pneumococcal pneumonia that mimics human disease; and (2) determine whether *Streptococcus pneumoniae* can: (a) translocate to the heart, (b) cause adverse cardiac events, (c) induce cardiomyocyte death, and (d) lead to scar formation during severe pneumonia in baboons. METHODS/STUDY POPULATION: Six adult baboons (*Papio cynocephalus*) were surgically tethered to a monitoring system to continuously assess their heart rate, temperature, and electrocardiogram (ECG). A baseline transthoracic echocardiogram, 12-lead ECG, serum troponin-I levels, brain natriuretic peptide, and heart-type fatty acid binding protein (HFABP) levels were obtained before infection and at the end of the experiment to determine cardiovascular damage during pneumococcal pneumonia. Animals were challenged with 10^8 colony-forming units of *S. pneumoniae* in the right middle lobe using flexible bronchoscopy. Three baboons were rescued with ampicillin therapy (80 mg/kg/d) after the development of pneumonia. Cardiac damage was confirmed by examination of tissue sections using immunohistochemistry as well as electron and fluorescence microscopy. Western-blot and tissue staining were used to determine the presence of necroptosis (RIP3 and pMLKL) and apoptosis (Caspase-3) in the cardiac tissue. Cytokine and chemokine levels in the heart tissue were determined using Luminex technology. RESULTS/ANTICIPATED RESULTS: Four males (57%) and three (43%) females were challenged. The median age of all baboons was 11 (IQR, 10-19) years old, which corresponds to a middle-aged human. Infected baboons consistently developed severe pneumonia. All animals developed systemic inflammatory response syndrome with tachycardia, tachypnea, fever, and leukocytosis. Infection was characterized by initial leukocytosis followed by severe leukopenia on day 3 postinoculation. Non-specific ischemic alterations by ECG (ST segment and T-wave fluttering) and in the pre-mortem echocardiogram were observed. The median (IQR) levels of troponin I and HFABP at the end of the experiment were 3550 ng/mL (1717–5383) and 916.9 ng/mL (520.8–1323), respectively. Severe cardiomyopathy was observed using TEM and H&E stains in animals with severe pneumonia. Necroptosis was detected in cardiomyocytes of infected animals by the presence of pMLKL and RIP3 in cardiac tissues. Signs of cardiac remodeling indicated by disorganized collagen deposition was present in rescued animals but not in the

other animals. DISCUSSION/SIGNIFICANCE OF IMPACT: We confirmed that baboons experience cardiac injury during severe pneumococcal pneumonia that is characterized by myocardial invasion, activation of necroptosis, and tissue remodeling in animals rescued by antimicrobial therapy. Cardiac damage by invading pneumococci may explain why adverse cardiac events that occur during and after pneumococcal pneumonia in adult human patients.

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Central autonomic network dysfunction implicated in alcohol-related intimate partner violence

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OBJECTIVES/SPECIFIC AIMS: Most incidents of partner violence occur when one or both partners have been drinking, however, the mechanism through which this association exists is unclear. The neural circuits that support self-regulation of emotion and social behavior, as well as autonomic influences on the heart, are co-localized in the brain and represent an integrated bidirectional regulatory system. These physiological regulatory processes are mediated by a neural substrate known as the central autonomic network which includes the peripheral autonomic nervous system. The central autonomic network modulates biobehavioral resources in emotion by flexibly responding to physiological arousal in response to changing situational demands, and serves a fundamental role in emotion regulation and goal-directed motor behavior, and this circuit can be indexed with heart rate variability (HRV). METHODS/STUDY POPULATION: In total, 17 distressed violent (DV) partners (11 females, 6 males) were matched to a sample of distressed nonviolent (DNV) partners (7 female, 6 males) were matched on age, sex, and relationship satisfaction and participated in a placebo-controlled alcohol administration study with an emotion-regulation task during which electroencephalography, HRV, and galvanic skin response (GSR) measures were collected. In the alcohol condition, participants were administered a mixture of 100 proof vodka and cranberry juice calculated to raise their blood alcohol concentration to 0.08%. In the placebo condition, participants consumed a volume of juice equivalent to that consumed in the alcohol condition, but without alcohol. Alcohol and placebo conditions were counter-balanced across participants as were the presentation of the blocks of evocative and neutral partner stimuli and emotion-regulation condition (watch vs. do not react). RESULTS/ANTICIPATED RESULTS: Results show that DV partners show greater cortical arousal than DNV partners on measures event-related spectral perturbations, which are mean log event-locked deviations from baseline-mean power at each frequency of the electroencephalography power spectra, when intoxicated and viewing evocative partner stimuli in the “do not react” emotion regulation condition. Results also show a statistically significant 2 (alcohol vs. placebo) \times 2 (watch vs. do not react) \times 2 (DV partners vs. DNV partners) interaction of the respiratory sinus arrhythmia measure of HRV when viewing evocative partner behavior ($F=7.102$, $p=0.019$, partial $\eta^2=0.353$). Findings indicate that DV partners have lower HRV than DNV partners across conditions, but particularly when acutely intoxicated and trying not to react to their partners’ evocative behavior. Similarly, results also show a statistically significantly 2 (alcohol vs. placebo) \times 2 (watch vs. do not react) \times 2 (DV partners vs. DNV partners) interaction on GSR ($F=71.452$, $p=0.000$, partial $\eta^2=0.749$). GSR findings indicate that DV partners also have lower GSR when acutely intoxicated and trying not to react to their partners’ evocative behavior. DISCUSSION/SIGNIFICANCE OF IMPACT: These results suggest that increases in intimate partner violence under acute alcohol intoxication may be the result of dysfunction of the central autonomic network, especially when DV partners are trying to suppress a behavioral response to their partners’ evocative behavior in conflict. The neurophysiological patterns evidenced by DV partners is consistent with a state of vigilance to threat, and reduced ability inhibit prepotent, but inappropriate responses. They also suggest that HRV may be an important target for intervention with partner with a history of intimate partner violence. One method may be heart rate variability biofeedback which has been shown to increase parasympathetic nervous system functioning, autonomic stability, and emotion regulation.

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Characterizing specialized pro-resolving lipid mediators and synthesis pathways in veterans with peripheral artery disease

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OBJECTIVES/SPECIFIC AIMS: Specialized pro-resolving lipid mediators (SPM) actively counter proinflammatory cascades. A deficit of SPMs is one possible mechanism through which inflammation leads to the development of atherosclerotic disease. The purpose of this study is to characterize the profiles